PTO 05-0679

CY=DE DATE=19910822 KIND=A5
PN=293 136

PROCESS FOR THE PRODUCTION OF (1R, 4S)-4-ACYLOXY-1-HYDROXYCYCLOPENT-2-ENES

[Verfahren zur Herstellung von (1R, 4S)-4-Acyloxy-1-hydroxycyclopent-2-enen]

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UNITED STATES PATENT AND TRADEMARK OFFICE
Washington, D.C. November 2004

Translated by: FLS, Inc.

PUBLICATION COUNTRY	(10):	DD
DOCUMENT NUMBER	(11):	DD 293 136
DOCUMENT KIND	(12):	A5
	(13):	
PUBLICATION DATE	(43):	19910822
PUBLICATION DATE	(45):	
APPLICATION NUMBER	(21):	DD C 12 P/338 345 8
APPLICATION DATE	(22):	19900302
ADDITION TO	(61):	
INTERNATIONAL CLASSIFICATION	(51):	C 12 P 7/62
DOMESTIC CLASSIFICATION	(52):	
PRIORITY COUNTRY	(33):	
PRIORITY NUMBER	(31):	
PRIORITY DATE	(32):	

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APPLICANT	(71):	PROCESS FOR THE PRODUCTION OF (1R, 4S)-4-ACYLOXY-1-HYDROXYCYCLOPENT-2-ENES

FOREIGN TITLE	[54A]:	Verfahren zur Herstellung von (1R, 4S)-4-Acyloxy-1-hydroxycyclopent-2-enen

[55]

The invention pertains to a process for the production of (1R, 4S)-4-acyloxy-1-hydroxycyclopent-2-enes, in which cis-1,4-dihydroxycyclopent-2-ene is reacted with a carbonic acid ester, according to the invention a carbonic acid vinyl ester, in the presence of a lipase. The desired product serves as the starting material for the synthesis of optically active prostaglandins and prostaglandin derivatives, which can be used as heart and circulatory medication and in veterinary medicine.

Patent Claims:

1. Process for the production of (1R, 4S)-4-acyloxy-1-hydroxycyclopent-2-enes of the general formula I, in which R^1 indicates n-alkyl, by the reaction of cis-1,4-dihydroxycyclopent-2-ene of the formula II with carbonic acid ester in the presence of a lipase at temperatures between 0 and 80°C, **thereby characterized** that a carbonic acid vinyl ester of the general formula III, in which R^1 indicates n-alkyl, as the carbonic acid ester.

2. Process according to Claim 1, **thereby characterized** that the reaction with the carbonic acid vinyl ester takes place in the presence of an anhydrous organic solvent.

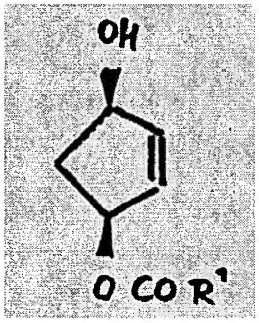
3. Process according to Claim 1, **thereby characterized** that the reaction with the carbonic acid vinyl ester takes place in the presence of a base.

4. Process according to Claims 1, 2 and 3, **thereby characterized** that the reaction with the carbonic acid vinyl ester takes place in the presence of an anhydrous organic solvent as well as a base.

1 page formulas attached

Area of Application of the Invention

The invention pertains to a process for the production of (1R, 4S)-4-acyloxy-1-hydroxycyclopent-2-enes of the general formula I,



in which R^1 indicates n-alkyl.

This type of compound is the starting material for the synthesis of optically active prostaglandins and prostaglandin derivatives, which can be used for the prevention and treatment of heart and circulatory disease, for gynecological indications, for treatment and prevention of stomach and intestinal ulcers in human medicine as well as birth and breast synchronization in animal production.

Characteristics of the Known State of the Art

The enzyme catalyzed transesterification of cis-1,4-dihydroxycyclopent-2-ene with carbonic acid esters, in particular with 2,2,2-trichloroethylacetate, in anhydrous organic solvent in the presence of a base and a lipase at temperatures between 0 and 80°C indeed leads to the formation of the desired compound with large enantiomeric excess (approx. 95% ee), however only in yields under 50% (DD-A1-264 707). The disadvantages of this process are

furthermore the use of the relatively expensive and difficult to remove 2,2,2-trichloroethylacetate and the relatively long reaction times.

Goal of the Invention

The goal of the invention is to discover an enantioselective synthesis of (1R, 4S)-4-acyloxy-1-hydroxycyclopent-2-enes of the general formula 1, which runs with cost effective acylation agent and in a short time, whereby the chemical yield at very large enantiomeric excesses should be improved.

Presentation of the Essence of the Invention

The task of the invention is to develop a process for the production of (1R, 4S)-4-acyloxy-1-hydroxycyclopent-2-enes of the general formula I, in which R^1 indicates n-alkyl, by enzymatic transesterification, whereby an acylation agent suitable for achieving this goal should be used.

This task is solved in that the meso-compound cis-1,4-dihydroxycyclopent-2-ene of the formula II (G.O. Schenk, D.E. Dunlap; Angew. Chem. **68**, 248 [1956]; C. Kaneko, A. Sugimoto, S. Tanaka; Synthesis **1974**, 876) is reacted with a carbonic acid ester, according to the invention with a carbonic acid vinyl ester of the general formula III, in which R^1 indicates n-alkyl, in an anhydrous organic solvent such as diethyl ether, 1,4-dioxane, tetrahydrofuran or toluene, preferably tetrahydrofuran, in the presence of a base such as pyridine, triethylamine, 4-N,N-dimethylaminopyridine or imidazole,

preferably triethylamine, or without the addition of base and in the presence of a lipase of animal, microbial or plant origins, preferably raw porcine pancreas lipase in the form of prepared pancreatine, or without organic solvent in the presence of a base of the above named type and a lipase of the above named type at temperatures between 0 and 80°C, preferably 25°C.

In this way (1R, 4S)-4-Acyloxy-1-hydroxycyclopent-2-enes of the formula I are obtained in acceptable chemical yields (about 60%) at very high enantiomeric excess (>99% ee). Additionally, by the selection of the reaction conditions the reaction to the desired product is technically easier to arrange.

Implementation Examples

Example 1

A solution of 1.0 g (10 mmol) cis-1,4-dihydroxycyclopent-2-ene (III), 6.02 g (70 mmol) vinyl acetate and 0.71 g (7.0 mmol) absolute triethylamine in 25 ml absolute tetrahydrofuran are reacted at 25°C with 5 g raw porcine pancreas lipase in the form of prepared pancreatine and stirred 2.5 hours at a temperature of 25°C. Thereafter the suspension is filtered and the filter residue is washed with acetic acid ethyl ester. The filtrate is concentrated in a vacuum. The residue is purified through flash chromatography. 0.921 g (65%) (1R, 4S)-4-Acyloxy-1-hydroxycyclopent-2-ene (I) is obtained as a colorless crystal of melting point 46°C to 48°C.

^{1}H-NMR-spectrum ($CDCl_3$): 1.58 ppm (1H, dt, J 15 Hz and 4 Hz, 5α-H); 1.86 ppm (1H, s, OH); 1.99 ppm (3H, s, OAc); 2.74 ppm (1H, dt, J 15 Hz and 8 Hz, 50 β-H); 4.65 ppm (1H, m, 1α-H); 5.42 ppm (1H, mm, 4α-H); 5.98 ppm (2H, dd, J 15 Hz and 6 Hz, -CH=CH-). $[\alpha]^{20}_D$ -65.1° (c=1,$CHCl_3$).

Enantiomeric excess: >99% (according to ^{19}F-NMR of the (+)-Mosher ester)

Additionally, 0.588 g (32%) cis-1,4-diacetoxycyclopent-2-ene is obtained.

Example 2

A solution of 0.8 g (8 mmol) cis-1,4-dihydroxycyclopent-2-ene (II), 6.32 g (55 mmol) vinylbutyrate and 0.58 g (5.7 mmol) absolute triethylamine in 25 ml absolute tetrahydrofuran is reacted at 25°C with 4 g raw porcine pancreas lipase in the form of prepared pancreatine and stirred 2.5 hours at a temperature of 25°C. Thereafter, the suspension is filtered and the filter residue is washed with acetic acid ethyl ester. The filtrate is concentrated in a vacuum. The residue is purified using flash chromatography. 0.747 mg (55%) (1R,4S)-butyroxy-1-hydroxycyclopent-2-ene (I) of boiling point 140°C (15 Pa, Kugelrohr).

^{1}H-NMR spectrum ($CDCl_3$): 0.84 ppm (3H, t, J 7 Hz); 1.36-1.81 ppm (3H, m, 5α-H CH_2); 2.04 ppm (1H, s, OH); 2.74 ppm (1H, dt, J 15 Hz and 8 Hz, 5β-H); 4.64 ppm (1H, m, 1α-H); 5.44 ppm (1H, m, 4α-H); 5.98 ppm (2H, dd, J 15 Hz and 6 Hz, -CH=CH-).

$[\alpha]^{20}_D$ -60.7° (c= 1, $CHCl_3$).

Enantiomeric excess: >99% (according to ^{19}F-NMR of the (+)-Mosher ester)

Additionally, 0.613 g (32%) cis-1,4-butyroxycyclopent-2-ene is obtained.

Example 3

A solution of 1.0 g (10 mmol) cis-1,4-dihyroxycyclopent-2-ene (II), 13.0 g (350 mmol) vinyl acetate and 0.71 g (7.0 mmol) triethylamine is reacted at 25°C with 5 g raw porcine pancreas lipase in the form of prepared pancreatine and stirred 2.5 hours at a temperature of 25°C. After analogous treatment to that in example 1, 0.807 g (57%) (1R,4S)-4-acetoxy-1-hydroxycyclopent-2-ene (I) is obtained.

$[\alpha]^{20}_D$ -64.4° (c= 1, $CHCl_3$).

Enantiomeric excess: >99% (according to ^{19}F-NMR of the (+)-Mosher ester)

Additionally, 0.745 g (40%) cis-1,4-diacetoxy-cyclopent-2-ene is obtained.

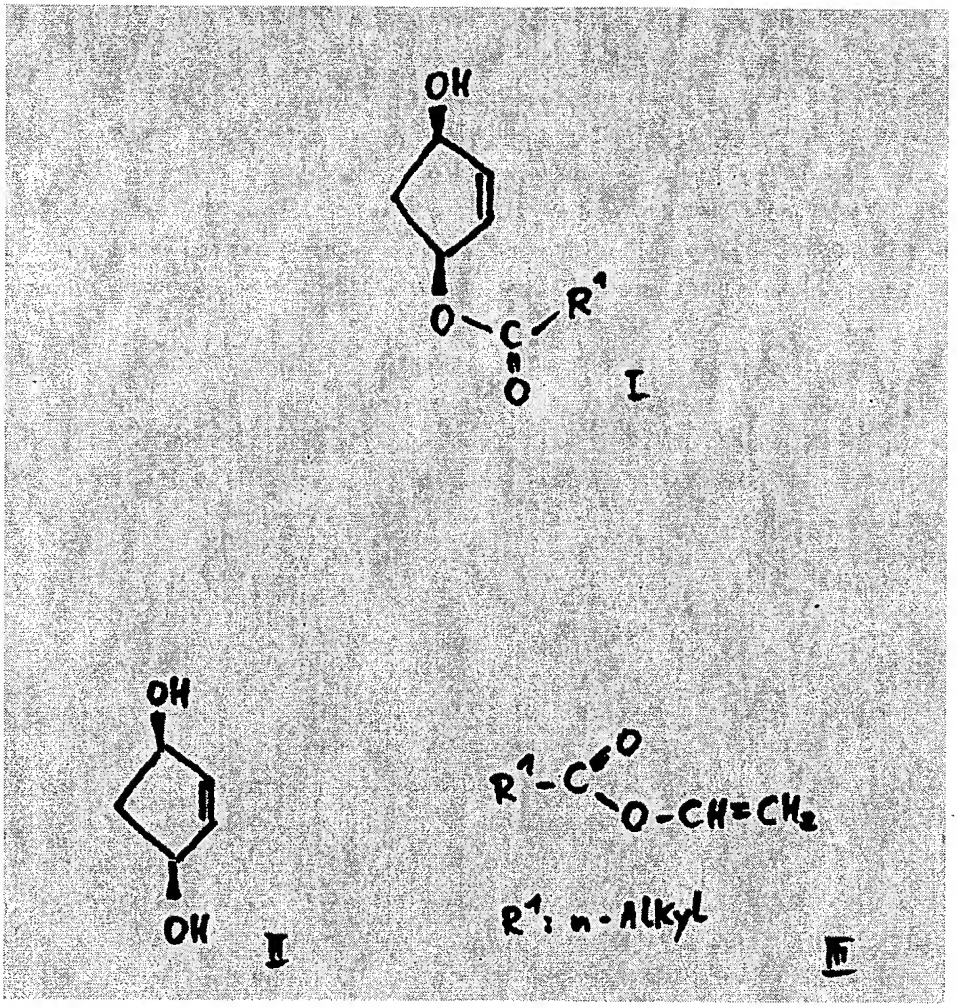
Example 4

A solution of 1.0 g (10 mmol) cis-1,4-dihyroxycyclopent-2-ene (II), 6.02 g (70 mmol) vinyl acetate and 25 ml tetrahydrofuran is reacted at 25°C with 5 g raw porcine pancreas lipase in the form of prepared pancreatine and stirred 2.5 hours at a temperature of 25°C.

After analogous treatment to that in example 1, 0.849 g (60%) (1R,4S)-4-acetoxy-1-hydroxycyclopent-2-ene (I) is obtained. $[\alpha]^{20}_{D}$ -64.6° (c= 1, $CHCl_3$).

Enantiomeric excess: >99% (according to ^{19}F-NMR of the (+)-Mosher ester)

Additionally, 0.563 g (31%) cis-1,4-diacetoxy-cyclopent-2-ene is obtained.


OH
O
C
O
R¹
I
OH
OH
II
R¹-C(=O)-O-CH=CH₂
R¹: n-Alkyl
III